Myc and Miz-1 have coordinate genomic functions including targeting Hox genes in human embryonic stem cells.

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Public Summary:
The Myc protein family are important cancer causing factors, but also have critical roles in normal stem cells including both human ES and iPS cells. However, the mechanisms by which Myc acts in both cancer cells and in iPS and ES cells are not well understood. Here we examined Myc function in human ES cells finding that the two main Myc family members, c-Myc and N-Myc, are both required for human ES cell growth. We further investigated Myc function in human ES cells by conducting the first ever genomics studies on Myc in human ES cells. Myc binds two main classes of genes in human ES cells--those that promote a stem like state and those that promote differentiation--with different consequences. Myc appears to turn on the stemness genes and turn off the differentiation genes. The function of Myc to turn off differentiation genes has long been postulated but the mechanism has remained elusive with most research focusing on Myc's function to turn genes on instead of off. We found using genomics studies that Myc relies on a novel cofactor called Miz-1 to repress the differentiation genes. Our studies were the first genomics studies on Miz-1 in any cell type. Overall these studies shed important light on how Myc functions in human ES cells to promote pluripotency via its cofactor Miz-1.

Scientific Abstract:
ABSTRACT: BACKGROUND: A proposed role for Myc in maintaining mouse embryonic stem (ES) cell pluripotency is transcriptional repression of key differentiation-promoting genes, but detail of the mechanism has remained an important open question. RESULTS: To test the hypothesis that the zinc finger protein Miz-1 plays a central role, in the present work we conducted chromatin immunoprecipitation/microarray (ChIP-chip) analysis of Myc and Miz-1 in human ES cells, finding homeobox (Hox) genes as the most significant functional class of Miz-1 direct targets. Miz-1 differentiation-associated target genes specifically lack acetylated lysine 9 and trimethylated lysine 4 of histone H3 (AcH3K9 and H3K4me3) histone marks, consistent with a repressed transcriptional state. Almost 30% of Miz-1 targets are also bound by Myc and these cobound genes are mostly factors that promote differentiation including Hox genes. Knockdown of Myc increased expression of differentiation genes directly bound by Myc and Miz-1, while a subset of the same genes is downregulated by Miz-1 loss-of-function. Myc and Miz-1 proteins interact with each other and associate with several corepressor factors in ES cells, suggesting a mechanism of repression of differentiation genes. CONCLUSIONS: Taken together our data indicate that Miz-1 and Myc maintain human ES cell pluripotency by coordinately suppressing differentiation genes, particularly Hox genes. These data also support a new model of how Myc and Miz-1 function on chromatin.